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Effect of Thrombolytic Therapy on the Evolution of Significant Mitral Regurgitation in Patients With a First Inferior Myocardial Infarction

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Objectives. This study was designed to test the hypothesis that reperfusion therapy with thrombolysis will prevent the development of significant mitral regurgitation in patients with inferior myocardial infarction.

Background. The value of thrombolytic therapy in patients with inferior or posterior wall myocardial infarction has been controversial. We hypothesized that successful reperfusion therapy with intravenous thrombolysis may reduce the incidence and severity of postinfarction mitral regurgitation in this patient group.

Methods. We prospectively studied 104 patients with a first inferior myocardial infarction. Thrombolytic therapy was administered to 55 patients (treatment group) 3.2 ± 2.1 h after the onset of symptoms. The other 49 patients formed the control group. Doppler echocardiographic color flow imaging was performed in all patients within 24 h, at 7 to 10 days and at 28 to 30 days after myocardial infarction. Significant mitral regurgitation was defined as moderate or severe (grade 2 or 3).

Results. No significant differences in baseline clinical characteristics were observed between the treatment and control groups. The overall incidence rates of significant mitral regurgitation at 24 h, 7 to 10 days and at 28 to 30 days were 10 (10%) of 104 patients, 18 (17%) of 104 patients and 11 (11%) of 100 patients, respectively.

Multivariate analysis reveals the following independent predictors of the occurrence of significant mitral regurgitation: female gender (at 7 to 10 days, odds ratio 5.3, 90% confidence interval [CI] 1.8 to 15.5; at 28 to 30 days, odds ratio 3.7, 90% CI 1.1 to 12.7), heart failure (at 7 to 10 days, odds ratio 7.7, 90% CI 2.2 to 26.9) and transient complete atrioventricular block (at 24 h of myocardial infarction, odds ratio 5.8, 90% CI 1.2 to 27).

Compared with the control group, the treatment group exhibited marked reduction in the incidence of significant mitral regurgitation at 24 h (16% vs. 4%; odds ratio 0.1, 90% CI 0.0 to 0.7); at 7 to 10 days (24% vs. 11%; odds ratio 0.3, 90% CI 0.1 to 0.9) and at 28 to 30 days (15% vs. 7%; odds ratio 0.4, 90% CI 0.1 to 1.6). Severe (grade 3) mitral regurgitation developed in five patients in the control group but in no patient in the treatment group.

Conclusions. Thrombolytic therapy in the patients with a first inferior myocardial infarction was associated with a reduced incidence of significant mitral regurgitation. These results support the use of such therapy in patients with inferior myocardial infarction.

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Mitral regurgitation is a serious complication of acute myocardial infarction. The presence of mitral regurgitation after acute myocardial infarction is associated with the development of hemodynamic deterioration, heart failure and poor outcome (1–5).

Recent reports have suggested that coronary revascularization with percutaneous transluminal coronary angioplasty (6–8) or coronary bypass grafting (1) may be useful in restoring mitral valve competence, improving hemodynamics and increasing survival in patients with ischemic mitral regurgitation. However, the possible protective influence of reperfusion therapy with thrombolytic agents has not yet been thoroughly elucidated.

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It is now well established that thrombolytic therapy administered soon after acute myocardial infarction reduces the mortality rate and preserves left ventricular function. Although this treatment has been widely accepted in patients with anterior wall myocardial infarction, its value in patients with inferior or posterior wall myocardial infarction has been controversial (9–11). Because ischemic mitral regurgitation frequently develops in patients with inferior and posterior myocardial infarction (12–15), we hypothesized that successful reperfusion therapy using intravenous thrombolysis may provide benefit by reducing the incidence and severity of postinfarction mitral regurgitation. The purpose of the present study was to test this hypothesis in patients with a first inferior or posterior wall myocardial infarction.

Methods

Study patients. Included in this study were patients <76 years old with acute inferior, inferoposterior, inferolateral or extensive posterior (inferoposterior-lateral) wall myocardial

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infarction. Exclusion criteria were 1) history of prior myocardial infarction, 2) history of rheumatic heart disease, heart failure, cardiac surgery or percutaneous transluminal coronary angioplasty, and 3) evidence of mitral valve prolapse or other mitral valve disease.

Inferior myocardial infarction was defined as 1) ischemic-type chest pain of >30 min duration, 2) new ST segment elevation >1 mV or new Q waves (>30 ms wide and >2 mV deep) in leads II, III and aVF on the surface electrocardiogram (ECG), and 3) serial elevation of serum cardiac creatine kinase MB levels.

Posterior myocardial infarction was defined as new ST segment elevation >1 mV or the development of new Q waves on ECG leads V_7, V_8 and V_9 (16).

Right ventricular infarction was diagnosed by ECG and echocardiography and defined as new ST segment elevation (1 mV) on ECG leads V_3R and V_4R (17).

Thrombolytic protocol. Patients eligible for thrombolysis were treated with either intravenous recombinant tissue-type plasminogen activator (rt-PA) or streptokinase. A total dose of 120 mg of rt-PA was given during a 6-h infusion, starting with a 10-mg bolus injection followed by a continuous infusion of 50 mg in the 1st h, 20 mg in the 2nd h and 10 mg during each of the next 4 h. Concomitantly, heparin was infused in a bolus injection of 5,000 IU and then continued at 25,000 IU/24 h. The dose was adjusted to maintain the activated partial thromboplastin time at 1.5 to 2 times the baseline level. Heparin infusion was continued for 5 days. Streptokinase (1.5 million U) was infused over a period of 60 min, followed by intravenous heparin for the next 5 days using the same protocol described for the rt-PA-treated patients. Each patient received oral aspirin (250 mg/day) beginning immediately on admission.

Thrombolysis was considered successful if abrupt relief of chest pain occurred within 90 min of treatment, associated with a decrease in the total ST segment elevation by ≥50% and an early peak (<12 h) of creatine kinase of myocardial origin (CK-MB).

Control group. This included all patients with a first inferior infarction ineligible for thrombolytic therapy because of either contraindications for thrombolysis or late arrival (>6 h) after onset of chest pain.

Echocardiography. Each patient underwent three echocardiographic examinations. Echocardiography was performed within 24 h after the onset of chest pain and was repeated at 7 to 10 days and at 28 to 30 days.

All echocardiographic studies included pulsed Doppler and color flow imaging as part of the study protocol. Standardized echocardiographic and Doppler examinations were performed using multiple orthogonal parasternal and apical views with the patient positioned in the left lateral decubitus position. Commercially available instrumentation was utilized (Hewlett-Packard) and was operated with either a 2.5-, 3.5- or 5-MHz transducer for the conventional echocardiographic images and a 2.5-MHz transducer for the color flow studies. Pulse repetition frequencies of 4, 6 and 8 MHz were available. A frequency of 4 MHz was most often used. Doppler color gain was optimized as described previously (18). Mitral regurgitation was considered present if blue, green or mosaic signals were seen originating from the mitral valve and spreading into the left atrium during systole.

Videotapes were carefully analyzed by consensus of two experienced observers (Z.V. and M.M.) who had no knowledge of the patients' clinical, ECG and angiographic data. For each patient, the maximal area of the regurgitant jet and regurgitant jet area/left atrial area in all three planes were measured. Severity of mitral regurgitation was graded on the basis of the method described by Helmcke et al. (19), which correlates Doppler color flow findings with angiographic scoring. No regurgitation was classified as grade 0; a mitral regurgitation jet occupying 5% to 19%, 20% to 39% and ≥40% of the left atrial area represented, respectively, mild (grade 1), moderate (grade 2) and severe (grade 3) mitral regurgitation.

Measurement of left ventricular function. Left ventricular ejection fraction was assessed in a subset of 77 patients by radionuclide ventriculography at predischarge examination (7 to 10 days). All radionuclide examinations were assessed by an experienced cardiologist who had no knowledge of the clinical data on the examined patient.

End points. The primary end point of the study was the development of significant mitral regurgitation (grade 2 or 3). Secondary end points were the development of mitral regurgitation of any grade, as well as in-hospital and follow-up events.

Statistical methods. The prevalence of potential risk factors for significant mitral regurgitation in patients with and without thrombolysis was compared. The chi-square test was used to compare the proportion of patients with a particular variable in the treatment group with that in the control group. The *t* test was used to determine differences between the mean values of continuous variables for the two groups. Multivariate logistic analysis was subsequently conducted to identify variables that were independently associated with the development of significant mitral regurgitation. The variables initially studied were age, gender, diabetes mellitus, presence of posterior wall infarction, presence of right ventricular infarction, congestive heart failure, any arrhythmias, complete atrioventricular (AV) block, postmyocardial infarction ischemia, coronary revascularization and administration of thrombolytic therapy.

Adjusted chi-square with $p = 0.15$ for entry and $p = 0.05$ for removal were used, with age and thrombolytic therapy forced into the model and other covariates examined in a stepwise manner. The LOGISTIC procedure of the Statistical Analysis System (SAS version 6) was used to evaluate risk coefficients and yield the individual estimated risk probabilities (20).

Results

Study patients. During the 18-month study period, 462 patients were admitted with documented myocardial infarction to the coronary care unit at the Heart Institute, Sheba

Table 1. Clinical Characteristics of 104 Patients*

	Thrombolytic Treatment (n = 55)	Control (n = 49)
Mean age ± SD (yr)	57 ± 12	62 ± 10
Female	13 (24)	12 (24)
Diabetes mellitus	10 (18)	5 (10)
Hypertension	15 (27)	9 (18)
Posterior MI	38 (69)	26 (53)
Right ventricular MI	17 (31)	9 (18)
LVEF (% ± SD)	54 ± 7	51 ± 7

*No differences were statistically significant. Data are presented as mean value ± SD or number (%) of patients. LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Medical Center, Tel-Hashomer, Israel. One hundred fourteen patients met the entry criteria for eligibility in the study.

Intravenous thrombolytic therapy was administered to 61 patients within 3.2 ± 2.1 h after onset of chest pain, streptokinase to 45 and rt-PA to 16 patients. Forty-six patients (75%) were judged to have successful reperfusion by clinical criteria. Fifty-three patients did not receive thrombolytic therapy (control group).

Because 6 patients from the treatment group and 4 patients from the control group were excluded because of inadequate echocardiographic imaging, the study group comprised 104 patients (55 patients treated with a thrombolytic agent and 49 control patients).

Three patients (one in the treatment and two in the control group) died after the second examination. One patient in the control group missed the follow-up examination. Thus, follow-up (28 to 30 days) was carried out in 100 patients.

Baseline characteristics. Table 1 presents the baseline clinical characteristics of the patients in the treatment and control groups. The two groups were generally comparable and contained a similar proportion of patients at increased risk.

Incidence of postinfarction mitral regurgitation. Table 2 shows the incidence and severity of mitral regurgitation among the study patients. Mitral regurgitation of any grade developed in 33% (34 of 104 patients) within 24 h; this proportion increased to 41% (43 of 104 patients), at 7 to 10 days and decreased to 33% (33 of 100 patients) at 28 to 30 days.

The overall incidence rates of significant (moderate or severe) mitral regurgitation were 10% (10 of 104 patients), 17% (18 of 104 patients) and 11% (11 of 100 patients) at the three study examinations, respectively.

Clinical predictors associated with the development of significant mitral regurgitation. Stepwise logistic regression analysis of the baseline clinical variables, interventions and in-hospital complications disclosed several independent risk factors associated with the development of significant mitral regurgitation. These risk factors are listed in Table 3.

Association between thrombolysis and the development of significant mitral regurgitation (Fig. 1). Compared with the control group, after adjustment for age, gender, heart failure and complete AV block, patients receiving thrombolytic therapy exhibited a markedly reduced prevalence of significant mitral regurgitation at 24 h (16% vs. 4%, odds ratio 0.1, 90% confidence interval [CI] 0 to 0.7); at 7 to 10 days (24% vs. 11%, odds ratio 0.3, 90% CI 0.1 to 0.9) and at 28 to 30 days (15% vs. 7%, odds ratio 0.4, 90% CI 0.1 to 1.6).

None of the patients who received thrombolytic therapy developed severe mitral regurgitation, whereas five of the control patients did (Table 2).

In-hospital events. In-hospital complications, medication and procedures in the two groups were generally comparable (Table 4). The prevalence of heart failure and arrhythmias was lower in the treatment group, but these differences did not reach conventional statistical significance (11% vs. 18% and 29% vs. 43%, respectively).

The incidence of complications such as postinfarction ischemia and the use of nitrates or calcium channel blockers, which may effect the occurrence and severity of mitral regurgitation, was similar in both groups.

Table 2. Incidence and Severity of Mitral Regurgitation Among 104 Patients

	Mitral Regurgitation				
	None	Mild	Moderate	Severe	Total
At 24 h					
Thrombolytic treatment	41 (76)	12 (22)	2 (4)	0 (0)	55 (100)
Control	29 (59)	13 (27)	7 (14)	1 (2)	49 (100)
Total	70 (67)	24 (23)	9 (9)	1 (1)	104 (100)
At 7 to 10 days					
Thrombolytic treatment	36 (65)	13 (24)	6 (11)	0 (0)	55 (100)
Control	25 (51)	12 (25)	7 (14)	5 (10)	49 (100)
Total	61 (59)	25 (24)	13 (12)	5 (5)	104 (100)
At 28 to 30 days					
Thrombolytic treatment	38 (70)	12 (22)	4 (7)	0 (0)	54 (100)
Control	29 (63)	10 (22)	2 (4)	5 (11)	46 (100)
Total	67 (67)	22 (22)	6 (6)	5 (5)	100 (100)

Data are presented as number (%) of patients.

Table 3. Odds Ratios for Development of Significant Mitral Regurgitation in the First Month After a First Inferior Myocardial Infarction

Clinical Variable	Odds Ratio	90% Confidence Interval
At 24 h		
Thrombolytic treatment	0.1	0.0 to 0.7
Complete AV block	5.8	1.2 to 27.0
At 7 to 10 days		
Thrombolytic treatment	0.3	0.1 to 0.9
Female	5.3	1.8 to 15.5
Heart failure	7.7	2.2 to 26.9
At 28 to 30 days		
Thrombolytic treatment	0.4	0.1 to 1.6
Female	3.7	1.1 to 12.7

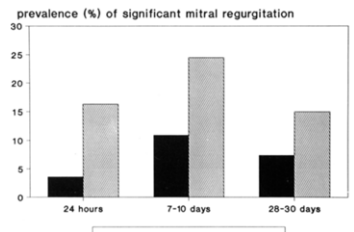
AV = atrioventricular.

Effect of coronary angioplasty on the severity of mitral regurgitation. Percutaneous transluminal coronary angioplasty was performed in eight patients. Before the procedure, four patients (two from the treatment group and two from the control group) had significant mitral regurgitation. Successful coronary angioplasty abolished the mitral regurgitation in two patients and reduced the severity of mitral regurgitation in one patient. The left circumflex coronary artery was involved in these patients. The single patient in whom coronary angioplasty did not reduce the severity of mitral regurgitation had total occlusion of the left circumflex artery and dilation was performed on a lesion in the left anterior descending coronary artery.

Discussion

The main finding of our study is that thrombolytic therapy during a first inferior myocardial infarction is associated with a reduced incidence and severity of ischemic mitral regurgitation.

Figure 1. Influence of thrombolysis on the prevalence of significant mitral regurgitation in 104 patients with a first inferior myocardial infarction.



Incidence and significance of postinfarction mitral regurgitation. Mitral regurgitation is a relatively common complication of myocardial infarction; recent reports (3–5,13–15,21,22) suggest that it has an incidence rate of 9% to 56%. In the present study, the incidence of significant (moderate or severe) mitral regurgitation was 10.6% at 24 h, increased to 17% at 7 to 10 days and was 11% at 28 to 30 days. When significant mitral regurgitation developed, it never resolved spontaneously and sometimes increased in severity from moderate to severe. Decreasing severity of significant mitral regurgitation was observed only after reperfusion with coronary angioplasty or bypass grafting.

Earlier studies (1–5) showed that the presence of mitral regurgitation after acute myocardial infarction is associated with severe heart failure and significantly influences short- and long-term prognosis. Mitral regurgitation may also reflect ongoing ischemia (3). In the present study, however, there were no significant differences in the prevalence of recurrent ischemic episodes or in the results of predischarge exercise tests between the treatment and control groups (Table 4).

Predictors for development of significant mitral regurgitation. Complete AV block was associated with significant mitral regurgitation at 24 h. This association may be partly explained by the development of AV dissociation. In addition, heart block during inferior myocardial infarction may be a marker for large infarction (23,24), which has been attributed to the development of mitral regurgitation after myocardial infarction (2). Women exhibited an increased incidence of significant mitral regurgitation at 7 to 10 and 28 to 30 days after infarction. The independent nature of this observation is in agreement with previous studies (1,3,4). Increased risk for complications and death in women after acute myocardial infarction has been demonstrated (25). The cause for the higher incidence of mitral regurgitation in women than in men remains unknown.

Table 4. In-Hospital Events and Interventions*

	Thrombolytic Treatment (n = 55)	Control (n = 49)
Complications		
AV block	14 (25)	7 (14)
Arrhythmias	16 (29)	21 (43)
Postinfarction ischemia	21 (38)	18 (37)
Heart failure	6 (11)	9 (18)
Mortality	1 (2)	2 (4)
Medications		
Nitrates	11 (20)	8 (16)
Calcium channel blockers	12 (22)	8 (16)
Beta-blockers	9 (16)	6 (12)
Revascularization		
PTCA or CABG	6 (11)	6 (12)

*No differences were statistically significant. Data are presented as number (%) of patients. AV = atrioventricular; CABG = aortocoronary bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty.

Heart failure was associated with the occurrence of significant mitral regurgitation at 7 to 10 days after myocardial infarction, when the greatest prevalence of mitral regurgitation was measured (Table 2). This finding is in accord with studies demonstrating a high incidence of congestive heart failure (3), a large infarction (2), a higher end-diastolic volume (5) and a lower left ventricular ejection fraction (5,21) among patients with mitral regurgitation after acute myocardial infarction. However, it is unclear whether mitral regurgitation or heart failure is the primary cause.

Effect of thrombolysis on ischemic mitral regurgitation. There are sparse and discordant data as to the effect of thrombolysis on the development of postinfarction mitral regurgitation. A preliminary report (22) from the Thrombolysis in Myocardial Infarction (TIMI) Phase 1 trial described 132 patients with a first myocardial infarction who received thrombolytic therapy. The presence of mitral regurgitation was independent of coronary artery patency before and after thrombolysis. Early mitral regurgitation resolved in 57% of patients within 10 days. This resolution was also independent of successful coronary artery reperfusion.

Hickey et al. (1) reported on the effect of thrombolytic treatment or emergency angioplasty, or both, in 63 patients with significant ischemic mitral regurgitation. In all but nine patients, reperfusion was achieved within 24 h of the onset of ischemia. These nine patients underwent urgent angioplasty within 21 days of infarction. In four of the nine patients receiving delayed reperfusion, mitral regurgitation resolved completely after reperfusion. Follow-up ventriculography demonstrated a significant reduction in regurgitation in the patients with successful reperfusion and a trend was perceived for improved short- and long-term survival with reperfusion therapy. Hickey et al. (1), however, did not clearly differentiate between the outcome of patients treated with thrombolysis versus angioplasty.

The mechanisms by which thrombolysis may prevent the development of mitral regurgitation are not clear. On the basis of current concepts of papillary muscle dysfunction (1,2,15), we speculate that successful reperfusion prevents the development of mitral regurgitation by limiting infarct size, attenuating stunning and preventing infarct expansion and dyskinesia, especially in areas of myocardium supporting the papillary muscles.

Limitations of the study. The major limitation of our study is the absence of a randomized controlled comparison. However, because thrombolysis is now firmly established as life-saving therapy for acute myocardial infarction, randomization of patients to this treatment has been rendered ethically unfeasible.

The lack of immediate coronary angiography is another considerable limitation. This procedure would have helped to correlate the prevalence and severity of mitral regurgitation with the success of lytic therapy, patency of the culprit infarct-related artery and possible value of late spontaneous recanalization in the absence of early reperfusion.

Another shortcoming is lack of data on left ventricular size and segmental wall motion. The differences in the distribution and severity of asynergy in relation to presence of mitral regurgitation may provide a firmer foundation for our observations. However, our study did not attempt to delineate the mechanism of ischemic mitral regurgitation, which is multifactorial and may vary depending on individual clinical characteristics.

Conclusions and implications. This study is the first to indicate the benefit of thrombolytic therapy in the treatment of ischemic mitral regurgitation in patients with acute inferior myocardial infarction. The best approach to ischemic mitral regurgitation is to prevent its occurrence. Thrombolytic therapy has several advantages over other means of treatment for ischemic mitral regurgitation. Thrombolysis is safer and may result in earlier reperfusion than occurs with other means. Reestablishment of blood flow in the target artery is associated with a high probability of recovery of valve competence and obviates the need for mechanical revascularization or valve procedures. In view of the present findings, we support the use of thrombolytic therapy in patients with inferior myocardial infarction.

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